III. REMARKS

Preliminary Remarks

Claim for Priority

Attached as Appendix A to this response is a copy of the Request for Filing filed with the present continuation application on September 15, 2003. The present application is identified as a continuation of parent U.S. Patent Application 09/053,152 filed April 1, 1998 on page 1, lines 7-14, and the application claims priority benefit of parent U.S. Patent Application 09/053,152 filed April 1, 1998, and of U.S. Patent Application 08/786,937 filed January 22, 1997, in section 9, on page 2, lines 28-30, of the Request for Filing. Recognition of the applicants' claim for priority benefit of parent U.S. Patent Application 09/053,152 filed April 1, 1998 is respectfully requested.

Amendment of the Specification

The first paragraph on page 1, which was previously amended by the amendment filed on September 27, 2005, is further amended to identify the current status of parent U.S. Patent Appl. No. 08/786,937, filed January 22, 1997 (abandoned).

Four paragraphs on pages 10 and 11 are amended to correct typographical errors and grammatical improprieties.

Supplemental Application Data Sheet

A Supplemental Application Data Sheet is submitted herewith that identifies the domestic priority information for the present application.

Amendment of the Claims

Claims 22, 29-31, 33, 34, and 36-39 are amended, and new claims 43-46 are submitted.

Upon entry of the amendment, claims 22, 26-34, and 36-46 will be pending.

The preamble of claim 22 is amended to be directed to a method of treating infertility comprising the specified elements; and claim 22 is further amended by inserting a comma after "antarelix."

Claims 29-31 and 39 are amended by replacing the term "LH-RH" with the term "LHRH", in accordance with the terminology of the specification, *e.g.*, at page 1, line 13, and claim 22.

Claim 33 is amended to describe a method wherein ovulation is induced by administering gonadotropins FSH or LH, as described in the specification, *e.g.*, at page 3, line 24, to page 4, line 2, which expressly describes administering exogenous gonadotropin to stimulate follicular development and induce ovulation.

Claim 34 is amended to describe a method wherein ovulation is induced by administering LHRH and/or LHRH agonist as described in the specification, *e.g.*, at page 4, lines 1-3.

Claim 36 is amended placing parentheses around the term "HCG" for clarity.

Claim 37 is amended by deleting the word "native." Support for the method of claim 37 is found in the specification, *e.g.*, on page 4, lines 4-25.

Claim 38 is amended to specify a method wherein FSH, LH, LHRH, or LHRH agonist is administered so that ovarian hyperstimulation syndrome is avoided as described in the specification, *e.g.*, on page 3, line 9, to page 4, line 25.

New claims 43 and 44 are directed to disclosed methods of Controlled Ovarian Stimulation (COS), as described, for example, on page 7, line 6, to page 8, line 15, and Table I, and correspond closely in subject matter to claims 22 and 39, respectively.

New claims 45 and 46 are directed to disclosed methods of treating fertility disorders treatable by controlled ovarian stimulation and assisted reproduction techniques, comprising the steps of the methods of independent claims 22 and 39, respectively, and further comprising performing assisted reproduction techniques following induction of ovulation as described in the specification, *e.g.*, in the paragraph bridging pages 4-5.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserves the right to pursue such subject matter in continuing applications.

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Patentability Remarks

Objection to the Specification

The specification is objected to as allegedly failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR § 1.75(d)(l) and MPEP § 608.01(o). Specifically, the examiner alleges that

(a) the reference in claim 33 to induction of ovulation by "recombinant LH,"

(b) the reference in claim 34 to induction of ovulation by "native LHRH,"

(c) the reference in claim 37 to administering "native LHRH or an LHRH antagonist ...so that luteal phase supplementation is avoided and negative effects of HCG are prevented during the luteal phase," and

(d) the reference in claim 38 to administering "recombinant LH, native LHRH or LHRH agonist...so that ovarian hyperstimulation syndrome is avoided,"

all are considered to lack antecedent basis in the specification.

The applicants submit that claims 33, 34, 37, and 38 are amended by deleting references to "recombinant LH" and "native LHRH," and that proper antecedent basis for the methods specified in claims 33, 34, 37, and 38 is found in the description of the invention provided by the specification as filed, as discussed in the preliminary remarks provided above. The applicants therefore respectfully request that the objection to the specification as allegedly failing to provide proper antecedent basis for the subject matter of 33, 34, 37, and 38 be withdrawn.

35 U.S.C. §112, First Paragraph/Enablement

Claims 22, 26-34 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification is considered to be enabling for a method for treating female infertility, but allegedly does enable one of skill in the art to practice the claimed method "for treating fertility disorders," because the claims encompass treating disorders that are causes of male infertility. The examiner lists the factors to be considered in determining whether a disclosure meets the

enablement requirement of 35 U. S.C. 112, first paragraph, which are described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. The examiner alleges the specification does not enable a person of skill in the art to which the claimed invention pertains to practice the invention commensurate in scope with the claims, and that consideration of the factors as they relate to the claimed invention leads to the conclusion that one of skill in the art would have to perform undue experimentation to practice the invention as claimed.

The applicants respectfully submit that the specification of the present application complies with the enablement requirement of 35 U. S.C. 112, first paragraph, because the description of the claimed invention provided by the specification enables one of skill in the art to perform the method of treating fertility disorders of claims 22, 26-34 and 36-42, to successfully treat various fertility disorders in both males and females without requiring undue experimentation.

With regard to the nature of the disclosed invention (factor 1), the amount of direction or guidance presented (factor 6), and the presence or absence of working examples (factor 7), the examiner characterizes the specification of the application as disclosing the administration of LHRH antagonist (cetrorelix) in combination with clomiphene and hMG or FSH (with or without HCG) to treat female infertility, and refers to Examples 1 and 2 of the application in support of this characterization of the disclosed invention. *See* the third paragraph of page 5. The examiner acknowledges that the specification enables one of skill in the art to practice the claimed method comprising administration of a combination of compounds resulting in controlled ovarian stimulation, to successfully treat female infertility, without having to perform undue experimentation. *See* the first paragraph of page 4. However, the examiner alleges that "the specification does not provide any competent evidence or disclosed tests that are highly predictive" that the claimed method will operate successfully to treat various fertility disorders in males as well as females. *See* the second paragraph of page 4. The examiner further alleges that

"there is no demonstrated correlation that the tests and results apply to the treatment of "fertility disorder" embraced by the instant claims," and especially, that "there is no support or evidence that the claimed combination therapy would benefit male infertility disorder." *See* the third paragraph of page 4.

The applicants submit that the specification as filed clearly describes using controlled ovarian stimulation (COS) in combination with assisted reproduction techniques (ART) to successfully treat both male and female fertility disorders. For example, in the Background of the Invention, the specification states that "reasons for unsuccessful attempts to establish pregnancy can be attributed equally to male and female disorders," and that many assisted reproduction techniques are available today that are used to induce follicular growth and obtain fertilizable oocytes. The specification describes a "current standard treatment" as comprising administering HMG and HCG in order to induce follicular growth and obtain fertilizable oocytes, recovery and fertilization of the oocytes, and replacement into the uterus to induce pregnancy (*see* page 1, lines 17-31). The specification expressly states that "[t]oday this treatment is applied to clinical conditions of male and female infertility," (*see* page 2, lines 1-2).

In the Summary of the Invention, the specification states that the claimed invention comprising the administration of an LHRH antagonist to suppress LH surge during controlled ovarian stimulation reduces the incidence of severe adverse events associated with currently used treatments to induce ovarian stimulation, and that the applicants' experimental results also demonstrate additional new advantages "for the treatment of male and female infertility," *see* page 3, lines 9-16). The specification further describes that ovulation induction using an LHRH antagonist to suppress LH surge during controlled ovarian stimulation in conjunction with assisted reproduction techniques such as extracorporeal fertilization, *e.g.*, *in vitro* fertilization (IVF) or fertilization by intra-cytoplasmic sperm injection (ICSI), facilitates fertility treatment for infertile and sub-fertile males. *See* page 4, line 14, to page 5, line 1. Furthermore, Example 2 of the specification expressly describes achieving a high pregnancy rate by performing the method according to claim 22 to obtain oocytes that were fertilized by ICSI, which is a treatment for male infertility or sub-fertilility. *See* page 10, line 20, to page 11, line 15. At the time of filing, persons of skill in the art recognized that a variety of fertility disorders in males, such as varicoceles (involving obstruction of testicular blood flow), oligospermia (low sperm count),

congenital absence of the Vas Deferans (preventing sperm transport), Young's syndrome (involving epididymal obstruction), and Kartagener's syndrome (causing immotile sperm), were treatable by a method of controlled ovarian stimulation in combination with assisted reproduction techniques such as extracorporeal fertilization (*e.g.*, IVF or ICSI).

The examiner has therefore incorrectly characterized the specification as only describing and enabling the claimed method for the treatment of female infertility, and as failing to provide direction, guidance or a working example enabling the claimed method to be used to treat male infertility. The claimed invention is described throughout the application and in the working examples as one that can be used to treat infertility in both males and females, as discussed above. In particular, one of skill in the art would regard the demonstration in Example 2 that the claimed method can be used in a COS/ART protocol comprising extracorporal fertilization to treat male infertility with achievement of a high pregnancy rate as clear evidence that the claimed method can be used successfully to treat a variety of fertility disorders in males.

With regard to the state of the prior art (factor 2), the examiner states that at the time of filing, persons of skill in the art recognized that female infertility could be treated by a method comprising administering a combination of hormones and agent that regulate hormonal production and/or activity selected from hMG, clomiphene, FSH, HCG, LHRH, LHRH agonists, LHRH antagonists, progesterone, and a combined oral contraceptive preparation, that induces or improves ovarian stimulation. In support of this position, the examiner has cited five publications published in the period from 1999 to 2003. *See* the first paragraph of page 5.

The references cited by the examiner were published from one to five years after the most recent priority date of the present application (*i.e.*, the April 1, 1998, filing date of parent U.S. Patent Appl. No. 09/053,152), and therefore are not representative of the state of the art at the relevant priority date. The applicants agree that at the time the priority application was filed, persons of skill in the art recognized that ovarian stimulation could be induced or improved by methods comprising administering a combination of hormones and compounds that regulate hormonal production and/or activity selected from hMG, clomiphene, FSH, HCG, LHRH, LHRH agonists, and LHRH antagonists. However, as discussed above, persons of skill in the art

would have known that such methods for inducing or improving ovarian stimulation can be used (in combination with ART) in treating infertility in males as well as in females.

With regard to the relative skill of those in the art, and the predictability or unpredictability of the art (factors 3 and 4), the examiner states that the relative skill of persons in the pharmaceutical art is high; and that there is a high level of unpredictability in the pharmaceutical art. *See* the second paragraph of page 5.

The applicants agree that the relative skill of persons in the pharmaceutical art is generally high, and that there is much unpredictability in the pharmaceutical art. However, one of skill in the art would recognize that multiple various infertility disorders in both males and females can predictably be treated successfully by a successful method comprising induction of ovarian stimulation such as the claimed method.

With regard to the breadth of the claims (factor 5), the examiner interprets the term "fertility disorder" in independent claims 22 and 39 as broadly including various disorders that cause infertility of men and women, including pelvic inflammatory disease, endometriosis, ovulation disorders, polycystic ovarian syndrome, abnormal cervical mucus, and antiphospholipid syndrome in women, and varicoceles, oligospermia, congenital absence of the Vas Deferans, Klinefelter's syndrome, Young's syndrome, and Kartagener's syndrome in men. *See* the fourth paragraph of page 4.

As discussed above, one of skill in the art at the time of filing would have recognized that all of the fertility disorders affecting males identified by the examiner except Klinefelter's syndrome (having an extra X chromosome) are treatable by a method of controlled ovarian stimulation in combination with assisted reproduction techniques such as extracorporeal fertilization (*e.g.*, IVF or ICSI). Therefore, one of skill in the art would reasonably have expected the claimed method to provide successful treatment for various disorders that cause infertility of males, as well as disorders that cause infertility of females.

The examiner concludes by arguing, with reference to factor 4 (predictability of the invention) and factor 8 (quantity of experimentation necessary), that the efficacy of the claimed invention in treating the various fertility disorders embraced by the claims "cannot be predicted

from a priori or the instant specification," but must be determined case by case "by painstaking experimental study." The examiner then alleges that the foregoing consideration of the eight factors described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) leads to the conclusion that one of skill in the art at the time of filing could not have practiced the claimed invention without performing undue experimentation.

For the reasons discussed above, the applicants submit that the specification of the present application clearly describes the claimed invention sufficiently and in such a manner that one of skill in the art would be able to perform the claimed method of treating fertility disorders to successfully treat various fertility disorders in both males and females without requiring undue experimentation. Accordingly, withdrawal of the rejection of claims 22, 26-34 and 36-42 under 3 5 U.S.C. 112, first paragraph, for alleged lack of enablement is respectfully requested.

35 U.S.C. §112, Second Paragraph

Claims 22, 26-34 and 36-38 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite because claim 22 refers to compounds using a trademark or trade name, such as A-76154, Nal-Glu, and 88-88.

The applicants respectfully submit that the names of LHRH antagonists specified in claim 22 are the compound names by which the LHRH antagonists are commonly known and referred to by persons of skill in the art. For example, the abstract of Nestor et al. (J. Med. Chem., 1992, 35:3942-8) refers to ganirelix; the abstract of Deghengi et al. (Biomed. Pharmacother., 1993, 47:107-10) refers to antarelix; the abstract of Rivier et al. (J. Med. Chem., 1992, 35:4270-8) refers to antide and azaline B, the abstract of Stoeckemann et al. (J. Cancer Res. Clin. Oncol., 1993, 119:457-62) refers to ramorelix, the abstract of Haviv et al. (J. Med. Chem., 1994, 37:701-5) refers to Nal-Glu and A-76154, and the abstract of Weinbauer et al. (Andrologia, 1993, 25:141-7) refers to antide and cetrorelix. Copies of the cited abstracts are attached. Evidence that the compound names specified in claim 22 are the names by which the specified LHRH antagonists are known in the art is also found in claims of many issued patents, in which the same terms are specified. For example, see claim 10 of U.S. Patent No. 6,077,523, which refers to cetrorelix, ramorelix, antide, azaline B, and ganirelix, and claim 1 of U.S. Patent No.

6,022,860, which refers to antide, antarelix, ganirelix, Nal-Glu, and cetrorelix. Withdrawal of the rejection of claims 22, 26-34 and 36-38, under 35 U.S.C. §112, second paragraph, as allegedly being indefinite in relation to the specified names of LHRH antagonists is respectfully requested.

Claims 37 and 38 are alleged to be indefinite in referring to "native" or "recombinant" LHRH or LHRH agonist, because antecedent basis for these terms in claim 22 on which claims 37 and 38 depend is considered to be lacking.

Claims 37 and 38 are amended by deleting the adjectives "native" and "recombinant;" and withdrawal of the rejection of claims 37 and 38 under 35 U.S.C. §112, second paragraph, for indefiniteness in relation to these terms is respectfully requested.

35 U.S.C. §102(a)

Claims 22, 28-32, 36, and 39-42 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Hwang et al. (2003).

As indicated on the Supplemental Application Data Sheet submitted herewith, and in the first paragraph of the specification as amended by the amendment and response filed on September 27, 2005, the present application claims priority benefit of the April 1, 1998, filing date of U.S. Patent Application No. 09/053,152, of which the present application is a continuation application. Accordingly, the Hwang et al. (2003) publication is not available as prior art. Withdrawal of the rejection of claims 22, 28-32, 36, and 39-42 under 35 U.S.C. § 102(a) as allegedly being anticipated by Hwang et al. (2003) is respectfully requested.

35 U.S.C. §102(b)

Claims 22, 26, 28 and 39-42 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Craft et al. (1999).

Claims 22, 27, 28, 36, 37 and 39-42 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Engel et al. (2002).

Claims 22, 33-38 and 39 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Engel et al. (WO 99/55357, published November 4, 1999).

With regard to the foregoing three grounds for rejection under 35 U.S.C. § 102(b), the present application claims priority benefit of the April 1, 1998, filing date of U.S. Patent Application No. 09/053,152, of which the present application is a continuation, as noted above. Accordingly, the Craft et al. (1999), Engel et al. (2002), and Engel et al. (WO 99/55357, 1999) publications are not available as prior art against the claims of the present application. Withdrawal of the rejection under 35 U.S.C. § 102(b) of claims 22, 26, 28 and 39-42 as allegedly being anticipated by Craft et al. (1999), of claims 22, 27-28, 36-37 and 39-42 as allegedly being anticipated by Engel et al. (2002), and of claims 22, 33-38 and 39 as allegedly being anticipated by Engel et al. (WO 99/55357, 1999), is therefore respectfully requested.

IV. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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